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A CONTRIBUTION TO THE PATHOLOGY OF TRAUMATIC EPILEPSY

Comprising the Report of the Microscopical Examination in Two Cases Operated upon by Trephining

BY

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A CONTRIBUTION

TO THE

Pathology of Traumatic Epilepsy,

COMPRISING THE REPORT OF THE MICROSCOPICAL EXAMINATION IN TWO CASES OPERATED UPON BY TREPHINING.

FOR the opportunity of presenting these cases I am indebted to Professor Starr, who gave me the clinical histories, and the portions of the brains removed at the operations for microscopical study. The impetus which localization has given to brain surgery, and its rather extensive application at the present time, lends some interest to the study of these specimens. But attention is more especially directed to the question as to whether certain minute, very delicate changes, rather difficult to recognize in the removed fragments of the motor zones in these cases, may be considered as underlying the phenomena of epilepsy. The clinical histories are as follows:

CASE I. *Trauma—General Convulsions Beginning in Left Arm—Splinter of Bone in the Brain Removed—Recovery—Recurrence of Fits—Death.*—A. G——, male, aged twenty-four, met with an injury in April, 1888, which produced a fracture of the skull on the right side, at about the middle of the coronal suture. After the injury he was ill with fever and delirium about six weeks, but gradually recovered. Three years after this injury he began to have convulsions, from which he had suffered at intervals up to April, 1892, when he was first seen. The attacks began with a movement of the left arm, and a sensation of numbness in the left hand, and with a turning of the head to the left; he then lost consciousness and the convulsion became general. He has had as many as

two fits in a day, and the longest interval during the year was nine weeks. He had three fits in March, 1892. He was very dull mentally, and had been treated with very large doses of bromide of potassium, which diminished the frequency of, but did not arrest, the fits.

Operation by trephining was performed by Dr. McBurney on April 2, 1892. The skull was opened at the point of fracture over the arm centre on the right side. The external table was found to be fractured, but the internal table appeared to be uninjured. The dura was very much thickened, and the pia and brain were decidedly œdematous and yellower than normal. The pulsation in the brain was greater around the softened discolored area than in it. This discolored area pitted upon pressure, and to the touch gave the impression as if a cyst lay beneath, but puncture in all directions with a hypodermic needle failed to reach any cyst. The wound healed easily. He had no paralysis, and in three weeks he was discharged from the hospital. At that time he had very much improved mentally, and had had no fits. Soon after leaving the hospital the fits began again, and in the summer they occurred with greater frequency than before the operation, and in August he died in convulsions.

CASE II. *Trauma—Spasms of Right Hand—Cyst Removed—Recovery for Six Months—Recurrence—Second Trephining—Recovery.*—Male, aged fourteen, at the age of four had a severe fall, fracturing his skull over the left coronal suture. As a result of this he developed right hemiplegia with partial right hemianæsthesia, but without any aphasia. Traces of this hemiplegia still remain. At the age of twelve and a half he had a second fall, hit upon his head, and soon after this he began to suffer from Jacksonian epilepsy. His fits always began with a tingling and spasm in the right hand, which extended to the arm and then down the right leg, the face being very rarely involved, though occasionally the head turned to the right. There was no loss of consciousness during the attack. It lasted about a minute, and he felt slightly weaker in the arm and leg after it. He has had as many as six attacks in a day. The boy was mentally very bright and

had no headache. Evidence of an old depressed fracture was found in the skull, the depression extending forward over the first frontal convolution, so that its position was decidedly anterior to the motor area of the arm. Medical treatment having failed to relieve these attacks, it was resolved to trephine. The point selected was the arm centre in the upper third of the central convolution, though its position was an inch and a half posterior to the position of the old fracture. Dr. McBurney operated at Roosevelt Hospital on January 30, 1892. On exposing the dura it was found adherent to the bone and did not pulsate. When the dura was laid back it was found adherent to the pia, which was thickened and opaque so that the brain was not visible beneath it. On dividing the pia a cyst was found lying beneath the surface of the brain, and from this a drachm of clear fluid was evacuated. The cyst had lain in the pia itself. The walls of the cyst were removed. A strand of thickened pia was found running forward toward the old scar. The opening in the bone was therefore enlarged in the direction of the old fracture until this was reached, and a second cyst was found beneath the old fracture. This cyst was also evacuated of about two drachms of fluid and its walls taken away. The brain beneath the cysts appeared to be somewhat atrophied but pulsated normally. It had an appearance of being slightly more yellow than normal brain-tissue, and the number of blood-vessels and capillaries over its surface seemed to be rather increased. The wound was closed and healed well, and from January 30, 1892, the date of operation, until April, the boy had no fits at all. He then returned to the clinic, complaining of a return of his old attacks. On examination of the head it was found that there was a small collection of pus beneath the scalp, over the site of the opening in the bone. This pus was evacuated and the small abscess-cavity at once healed. From that date until August, 1892, the boy had no attacks. Then his attacks began again, and increased in frequency until in December he was having three or four daily. These attacks began with tingling and twitching in the right hand which extended up the arm and shoulder, then down the side to the leg, arm and leg twitch-

ing together for the space of from five to fifteen minutes. Subsequently to the attacks both arm and leg were slightly paretic, the face never being involved, and consciousness not being lost. The use of bromides during this period had no effect upon the increase of the attacks, and he was therefore again advised to go into the hospital for operation. On January 7, 1893, Dr. McBurney operated. On exposure of the shaven head the scalp was seen to be thick and tense, so that at no place was there any perceptible depression around the old scar or over the defect in the bone. Pulsation of the brain was perceptible by palpation over the area from which the bone had previously been removed, and which corresponded to the arm centre. The tissues were very much thickened, and it was thought best to avoid their direct incision. A semilunar incision was therefore made, the summit of which passed somewhat more to the left of the median line than the preceding incision and by dissecting up its anterior and posterior portions, the healthy bone below the old trephine was reached, the scalp being carefully dissected away from the old scar-tissue. A triangular opening was then chiselled in the bone about an inch and a half long and three-fourths of an inch wide. The bone was found to be closely adherent to the dura. The dura was seen to be thickened, and on being divided and turned back it was closely adherent to the pia. The pia and brain were found to be welded together in a thick connective-tissue mass. Palpation of this gave the impression of fluid beneath it. Puncture with a hypodermic syringe brought away a small amount of clear serous fluid from a cavity about half an inch beneath the cortex. Incision was made into this cavity through the brain above it. When the brain-tissue was incised it was found to present an abnormal appearance. There was no clear line of demarcation between the cortex and the white matter beneath it, but a connective-tissue mass had taken the place of the cortex. This mass of tissue was therefore excised, a piece of a lens shape, about an inch long by half an inch wide, being removed. It appeared to be scar-tissue. The second puncture with a hypodermic needle, at a point an inch farther forward, revealed the

presence of another cyst, and the incision in the brain was therefore carried forward so as to empty this. Hemorrhage was pretty free, but after the scar-tissue had been excised the sides of the wound in the brain was seen to consist of fairly normal gray and white substance. The wound was packed with iodoform gauze and dressed antiseptically. The next day the boy was very comfortable, had no paralysis or anæsthesia. Within two weeks the wound had healed. He has had no attacks up to March, 1893.

Microscopical Examination. — In describing these morphological changes in the motor cortex, which harmonize very well with the symptoms of epilepsy, it is of especial importance to preface the details of the examination with some general remarks about the technical limitations of investigations in the finer pathology of the cortex, and the extreme difficulties of detecting and attaching significance to the very early and subtle changes in the cortical elements. In such a preface the investigator should indicate the great caution and most refined technique which a study of minute cortical changes demands; for then the reader will appreciate that the observer has guarded against mistaking for lesions entirely artificial changes, or normal structures which, especially in the cortex, are by no means easy to define.

The difficulty in the way of research in cortical pathology is the complexity of the brain cortex; it is most supremely highly organized, and is far beyond all other organs and tissues in the textural delicacy of its anatomical elements and complexity of their arrangement. In most of the other organs the structure of the parenchyma is comparatively simple, and the stroma is arranged in such a way that there is a contrast between the two in the sections; thus in the kidney or liver, for example, the changes in the stroma or in the parenchyma attending a chronic inflammation may be determined very accurately. The stroma is so distinct from the parenchyma, and its distribution is so readily followed, that a very beginning of an increase in its substance may usually be easily and positively recognized. In the same way the distinctive distribution of the comparatively simple par-

enchyma cells permits early changes in them to be determined with but little difficulty.

When we come to the brain cortex, however, the contrast between stroma and parenchyma, which in other organs affords most valuable topographical aid, is lost, and the determination of changes in either stroma or parenchyma is correspondingly difficult. For in the brain cortex the neuroglia and ganglion cells, corresponding respectively to the stroma and parenchyma of other organs, are not only more intricately constructed, but are diffusely arranged. The neuroglia and ganglion cells are mingled together in a most intricate way, and are surrounded by a great wilderness of processes derived from both, which forms a very large part of what is conveniently called the basement substance of the gray matter.

Thus it can be understood what a difficult matter it is to determine any beginning increase or proliferation of the neuroglia, which in ordinarily stained sections presents itself as multitudes of small round nuclei scattered all through the gray matter, without any boundaries or limitations. This problem of the determination of a very early increase in the neuroglia becomes the more baffling because, as a rule, this tissue grows so slowly that the all-important criterion of the proliferation of cells, namely, the phases of karyokinesis, are difficult to find.

The investigation of minute and early changes in the other intrinsic element of the cortex—the ganglion cell—is rendered difficult by the presence of artifacts or artificial changes occurring after death. The structure of the ganglion cell is so delicate and intricate, and the cortex is so slowly permeable to the bichromate solutions, that a number of post-mortem changes are liable to occur in the cell or are induced by the action of the hardening agents. Such artificial changes may simulate very closely the results of disease, and when these artificial changes are present in a cortex with suspected disease of the ganglion cells, it becomes exceedingly difficult to understand the lesions, or to determine in what degree the changes are due to disease and in what degree to artificial conditions.

With the best of care we can recognize, after all, but the

coarser and grosser lesion in the ganglion-cell body, which is only a part of the cell. Changes in the great forest of processes of the cell, representing a volume of protoplasm fully as large, if not larger, than the cell body itself, are beyond our cognizance even with Golgi's methods, which seem to be of little service in showing minute changes in the ganglion cells. The aid of mitosis as an index of pathological changes in the ganglion cells is also absent, since the latest studies on this subject show that the ganglion cells seldom if ever proliferate.

Thus, owing either to perplexing artifacts, or to the inherent complexity of the cortex, its more minute changes seem beyond recognition at present, and when we do detect cortical disease processes it is only after they have gone on to some considerable extent beyond the initial stages, and have become rather coarse, extensive, or materially destructive. Since the wonderful revelations of the Golgi methods, one can reasonably enough conceive that changes may occur in the cortex which are of the greatest etiological significance, but so subtle that they are entirely hidden from our view.

It certainly seems appropriate, therefore, to speak with all this detail about these peculiar difficulties in the way of pathological investigation of the cortex, for if real advances are to be made in the finer pathology of the cortex its difficulties of investigation should be appreciated, and if the lesions to be described in these particular cases are to be at all considered as underlying the phenomena of epilepsy, we must approach the problem with all possible caution. I also wish to show that the material placed at my disposal by Professor Starr has such great advantages for investigation, both in its structure and preparation, that the difficulties and errors in determining early cortical changes are considerably reduced.

From the fact that these minute fragments of the cortex were immediately transferred from the living body to the hardening fluid, the changes in the ganglion cells are especially significant, for the element of artificial change incident to post-mortem alteration or the process of hardening larger portions of the cortex, which frequently interferes with making positive statements about the minute

changes in the ganglion cells, is more thoroughly excluded than in the material from an ordinary post-mortem examination. Even allowing for the fact that Müller's fluid does not preserve the ganglion cells perfectly, the damage to the ganglion cells, presently described, must have existed during life.

Microscopic Examination of Case I.—We may now go on with the detailed microscopical examination of the removed portion of the brain in Case I., and this comprises a description of: 1. A rigid plate of connective tissue acting as a foreign body and pressing against the brain. 2. Changes in the pia mater. 3. Certain lesions of the cortex of the brain, consisting of both changes in the ganglion cells and in the neuroglia.

Description of the Inwardly Projecting Plate of Connective Tissue Indenting the Surface of the Brain.—The removed portion was hardened in Müller's fluid plus one-sixth its volume of strong alcohol for three weeks. The specimen was very small, measuring about ten by six millimetres in diameter, and its central portion furnished about one hundred sections which were cut in series and stained double with hæmatoxylon and eosin, and by the picro-acid-fuchsin method.

Sections from the centre of the specimen, when reconstructed, show that a tiny plate of very dense, partially calcified connective tissue projected obliquely downward, apparently from the dura mater against the surface of the brain. Here the plate is firmly attached to a minute localized patch of thickened pia mater, and seems directly or indirectly to have pressed on the brain, for the cortex shows an abrupt little pit or depression (see Fig. 1) just beneath the inwardly projecting plate. This cortical depression corresponding to the plate is cone-shaped (with the apex projecting inward), and has approximately an altitude of three and three-fourths mm. and a base four to five mm. in diameter.

In the individual sections from the centre of the specimen the plate of connective tissue appears as a very dense, finely lamellated, partially calcified spiculum about three-fourths of a millimetre broad and three millimetres long (see Fig. 1, *xx*). At its inner extremity the spicu-

lum has a globular enlargement and the lamellæ do not run parallel as in the outer portion, but pass in various directions mostly concentrically arranged about a tiny central nodule or core. The outer end of the spiculum is entirely free in all of the sections, so that it is difficult to determine what the spiculum is a part of, or where it grew from. The inner end of the spiculum is attached in all directions by many diverging fascicles of the thickened pia mater.

As the sections approach the margin of the specimen

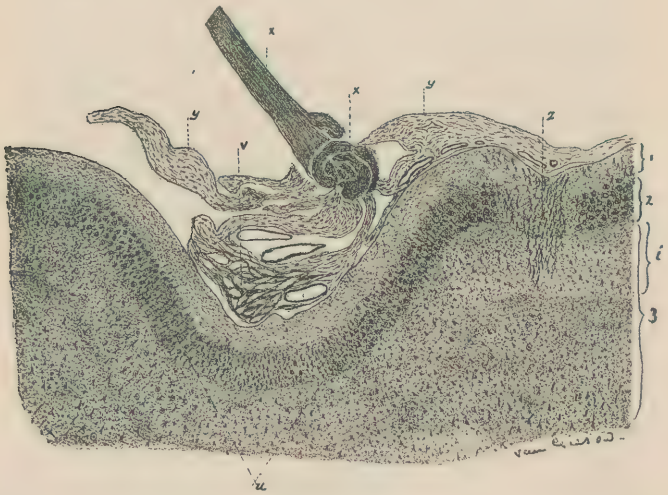

FIG. 1.—From the Centre of the Removed Portion of the Brain in Case I. The topographical relations of the rigid calcified spiculum of connective tissue, the thickened pia mater, and the depressed region of the cortex, are seen: *xx*, calcific spiculum of connective tissue; *yy*, moderately thickened pia mater; *z*, anastomosing wedge-shaped group of capillaries passing into the cortex from the pia mater. 1, 2, and 3, first, second, and third layers of the gray matter; *i*, upper portion of the third layer.

at one side the plate grows a trifle smaller, but still persists to the free edge, so that it seems probable that not all of the plate was removed at the operation. At any rate, it may be said that the removed portion was not large enough to completely surround the plate. From the very dense structure of this connective tissue, and from the fact that the edge of the microtome knife was turned in cutting the sections, this plate must have formed a fairly rigid body.

The Changes in the Pia Mater.—The pia mater, not only at the attached end of the spiculum, but for some little surrounding distance (say three to four millimetres), shows the lesions of chronic meningitis, or productive or hyperplastic inflammation of the pia mater (Fig. 1, *yy*). The pia mater in the region contains an increased amount of connective tissue, which consists of fibro-blasts in different stages of development, but most of them show the more mature or final stages. The resultant thickening of the pia mater, however, is only of a moderate degree, and has not gone on to the extent of obliterating the two layers of the membrane. The inner vascular layer still presents its normal features, although in places (see right-hand portion of the pia mater in Fig. 1) the vessels appear to be somewhat diminished in number.

The meshes of the inner layer of the pia mater in the depressed region of the cortex are distended and form a network (Fig. 1, *vv*) filled with extravasated red blood-cells. This extravasation of blood, as well as some minute hemorrhages in the gray matter, seem to be of artificial origin, and are very likely referable to the manipulation in the removal of the specimen at the operation.

The Lesions of the Cortex.—The lesions of the cortex in this case might easily escape detection without the most careful scrutiny and technique. There are hardly any gross changes in the cortex which would attract attention with the low power, and it is only with the oil immersion lens that slight changes in the neuroglia cells and scattered damaged ganglion cells become fully apparent. These cortical changes are very minute and not at all striking, and yet they are none the less definite and significant.

The Ganglion Cells.—The ganglion cells are affected by a series of degenerative changes which in their most advanced stages result in an almost complete dissolution of the cell, and yet this degeneration is not extensive enough to involve the cells so universally as to interfere with their topographical distribution. Besides this, most of the damaged cells are in the earlier stages of the degeneration, so that they still retain their form and appropriate position. Thus in reconnoitring the sections with

the lower powers the ganglion cells do not appear deficient in number; they are properly arranged and their several layers are perfectly distinct. The following description applies to all of the ganglion cells excepting the layer of small pyramids. For especial reasons this layer will be dealt with separately later on.

It will be convenient to describe the appearance of the nucleus and protoplasm of the degenerated ganglion cells separately. The prevailing form of nuclei shows a distinct peripheral zone, indicating the nuclear membrane: just inside of the nuclear membrane is a narrow clear zone surrounding the chromatic elements of the nucleus, appearing in the form of a skein of finely dotted interlacing filaments which show the usual thickened appearances at the nodal points and surround unstained interstices. The nucleolus is seen in most of these skein-like nuclei, and both the nucleolus and the character of the skein show no variations relating to the different degrees of dissolution of the ganglion cells. In both the early and ultimate stages of the degeneration the form of nucleus, as shown in Figs. 2, 3, and 4, remains about the same in all of the cells.

This particular form of nucleus in some of the cells is a trifle suggestive of one of the initial stages of karyokinesis, but none of the other stages of mitosis are present, so that this appearance of the nucleus must be regarded as an indication of retrogressive changes. There are no indications of mitosis in any of the ganglion cells, and this agrees with one of the latest papers on the ganglion-cell reproduction by Fürstner and Knoblauch (*Archiv. of Psych.*, xxiii., 1).

Some different appearances of the nucleus are shown in Fig. 2, in the cells *v*, *w*, and *y*. The nucleus of the cell *w* has its chromatic elements resolved into a number (some twenty to twenty-five in optical section) of larger and smaller globules or disks resembling very much the ordinary nucleolus. In the cells *y* and *v* the chromatic substance is collected into thickened strands, or large lump-like masses.

The protoplasm of the cells shows a series of changes which finally result in an entire disappearance of the cell

body—for a very complete series of intermediate stages can be observed between the slightly and most completely degenerated cells. The earlier stages of degeneration consist in larger and smaller solutions of the sub-

FIG. 2.—Various Phases of the Earlier Stages of the Degeneration of the Ganglion Cells. The thin lines enclosing the cells *w* and *u* represent the pericellular spaces; the cells *x* and *y* show the earliest stages, *w* and *s* later stages, and *k* shows the ultimate destruction of the whole of the ganglion-cell body, leaving nothing but the nucleus lying in an empty space.

stance of the cell, so that hollow-looking vesicles appear in the cell body. Such cells are shown in Fig. 2, *x* and

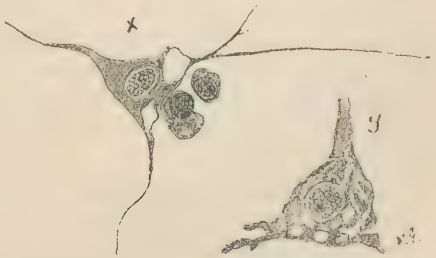

FIG. 3.—Other Phases of the Degeneration of the Ganglion Cells. The cell *x* shows a liquefied vesicle at the junction of two processes with the cell body and three small round cells crowded in the pericellular space; the cell *y* shows a series of liquefying seams or channels.

y, Fig. 3, *x*, and Fig. 4, *a*. The cell *x* in Fig. 2 also shows a ragged or roughened profile at one margin of the cell body. These vesicles frequently appear at the junction of one of the larger processes with the cell body, as

in Fig. 3, *x*, Fig. 4, *a*, or in the process itself some little distance from the cell (Fig. 4, *a*).

In a somewhat later stage, by the increase of these vesicles, and by their apparent coalescence, the cell body becomes more reduced in volume, deformed in its contours, and loses its processes. Besides the vesicles, liquefied seams and communicating channels also appear and contribute their share toward the destruction of the cells.

A very beautiful example of these channels or seams is shown in Fig. 3, *y*. This is one of the very large ganglion cells peculiar to the deeper layers of the motor zone, and it was situated on the extreme edge of the section, so

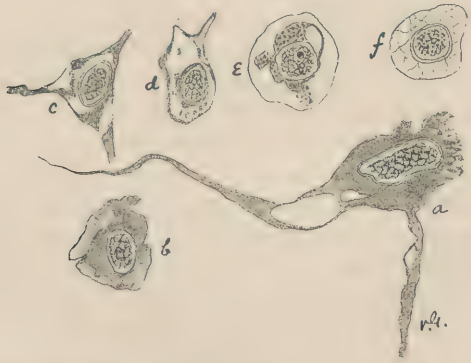

FIG. 4.—Other Variations of the Phases of Degeneration of the Ganglion Cells described in Figs. 2 and 3.

that it must have been immediately fixed by the hardening solution, and may be regarded therefore as showing very nearly the same condition possessed during life.

The cell *c*, Fig. 4, also shows a somewhat similar condition and illustrates how the apical process is being separated from the cell; the protoplasm surrounds the nucleus as a deformed or deficient mass such as is shown in Fig. 2, *w* and *s*, and Fig. 4, *b*.

In some of the degenerated cells the protoplasm at the bounding surface becomes frayed out, or loosened from the cell body in little granular islands or cord-like masses, while the remainder of the cell body may be comparatively intact. This is represented in Fig. 2, *u*, and in Fig. 4, *a*. The cell *a*, Fig. 4, is again one of the very

large cells in the deeper layers, and was situated just at the free edge of the section, so that it must have been fixed in a perfectly natural condition.

In still others of the ganglion cells the protoplasm is studded with irregularly distributed shining dots. In most of the cells affected in this way, and they are comparatively few in number, these dots seem akin to and react like hyalin material, and their appearance is shown in Fig. 2, *v*, *y*. These hyalin dots are present in both the slightly and severely damaged cells (Fig. 4, *e*).

In focussing on the surface of the cell *z* in Fig. 2, some larger lump-like hyalin masses were noted.

Thus far, to the rather restricted extent that we are able to recognize them, the beginning and most limited changes in the ganglion-cell body have been described. There were larger and smaller vesicular or channel-like solutions of the substance of the cell body, and a tendency toward disappearance or separation of the processes.

We may now go on with the consideration of the final and more grossly destructive phases of the ganglion-cell degeneration. Some of these cells undergoing the later stages of the degeneration are reduced to a mere shell or skeleton of the former cell; the outline of the cell is preserved, but the cell is hollow; the bounding surfaces are intact, and enclose the nucleus lying in an empty space or surrounded by a few shreds or granules of the former protoplasm (see Fig. 2, *k*, and Fig. 4, *f*). This condition seems to result from the extension and coalescence of the liquefaction seams and vesicles already described, and it is easy to trace the extension of the changes in the cell *y*, Fig. 3, to the cell *d*, Fig. 4.

These skeleton cells, when followed still farther in their degenerative course, show gradual dissolution and disappearance of the bounding shell, so that ultimately nothing remains of the cell but the nucleus, which lies bereft of protoplasm in the space once occupied by the ganglion cell (Fig. 2, *k*; Fig. 4, *f*).

Another way in which the ganglion cell ultimately becomes reduced to a mere nucleus is not so much by a solution of the protoplasm internally, as just described, but by a direct abstraction of portions of the external zones of the cell body. There is at first a slightly roughened sur-

face of the cell, at some portion of its extent, with a fraying out of shreds and most minute fragments of protoplasm into the pericellular space. Then there is a tendency toward a distinct sequestration of a portion of the protoplasm (Fig. 4, *b*, *e*), so that the cell body grows smaller and smaller as the solution of its substance proceeds from without inward. Thus the cell becomes deformed and atrophied; it loses its processes, and the pericellular space sometimes contains minute fragments of the loosened protoplasm (Fig. 4, *e*). Ultimately the cell becomes reduced to a naked nucleus lying in the pericellular space, as just described (Fig. 2, *k*; Fig. 4, *f*).

Very often this wasting away of the cell body from without inward is also combined with the liquefaction vesicles and channels or other forms of degeneration in the interior of the cell body (Fig. 4, *a*).

The ultimate fate of these nuclei, bereft of the ganglion-cell body, cannot be determined positively, but some of them become destroyed. The nuclear membrane and chromatin skin become disintegrated, and finally nothing is left but some fragments of the chromatin elements, surrounded by a complete or incomplete ring, which still take up the color of the nuclear dyes.

This description of the changes in the ganglion cells refers to the deeper layer of cells, and especially to the very large ganglion cells of the fourth layer, characteristic of the motor zone. The very large size of these cells renders the detection of the degenerative changes much more positive than in the other small cells. To be more certain of the ante-mortem origin of these lesions in the cells, as many as possible were selected for study in glycerine mounts at the extreme edge of the specimen, where they must have been immediately fixed in a natural condition. The spaces about these cells are small, and altogether the element of artificial changes may be more thoroughly excluded from them than in the much smaller cells.

One of the most striking features of this degeneration of the ganglion cells is the extensive involvement of these very large cells of the fourth layer. It may be that this feature is so evident from the fact that the degenerate

changes are so much easier to recognize in these cells, but it would appear as if they were especially selected by the degeneration. At any rate very few of the large cells are left intact, they show quite universally one phase or another of the degenerative changes. In cutting out the fragment at the operation, the knife seems to have sliced it off just at or below this layer of cells, so that very many of them lie right at the edge of the sections. Many of the smaller cells of the third and fourth layers, however, show precisely similar degenerative changes. There are many normal ganglion cells in deeper layers, and the degeneration affects apparently, excepting the very large cells, only isolated or small groups of cells here and there, and yet the aggregate number of the damaged cells must be very large.

Still another feature about the ganglion cells remains to be described. This consists in the accumulation of clusters of from one to four or five small round cells crowded together in the pericellular spaces of both the diseased and normal cells. These cells have a very thin envelope of protoplasm, and they are generally situated at the base of the cell. These cells are not infrequently found in brains with normal ganglion cells, and which have given no symptoms, and in the present case I am unable to interpret their meaning or determine what kind of cells they are.

We may now describe the layer of small pyramids which has been held apart from the deeper layers, because the element of artificial changes cannot be as positively excluded. The small pyramids are quite universally altered, and but a very small number of natural cells are found in the sections. The nucleus, surrounded by little if any protoplasm, lies in a rather large, empty, pericellular space, as shown in the right-hand portion of Fig. 6. But just such a picture of the small pyramids as this is generally found in any cortex, unless prepared by especial methods, and is generally to be regarded as largely of an artificial character. The small pyramids are especially prone to artificial changes, apparently from their very small size, which seems to render them correspondingly liable to shrinkage. Artificial changes in this case, however, must be considered reduced to a minimum, and

these alterations in the small pyramids in this case are not present in the sections of the motor cortex of an electrically executed criminal, prepared in the same way and studied along with this case as normal control sections. So that, while there may be reason in this instance for regarding these changes in the small pyramids as the results of actual disease, there is still doubt about it, and I prefer to disregard or exclude the small pyramids entirely from the larger deeper cells where the lesions are definite, positive, and significant.

The Pericellular Spaces.—There is very little to say about the lymph-spaces of the ganglion cells. They show no striking changes and are not enlarged. The space about the deeper cells fits fairly closely, and the relation of the cells and spaces is especially well preserved. The spaces of many of the degenerated cells appear very large, but this effect is produced by the atrophy of the enclosed cell.

The basement substance of the cortex, consisting, as it does, largely of the processes of the ganglion cells, must contain changes corresponding to the degenerated and destroyed ganglion cells, but such a lesion is entirely too subtle to be recognized at present even with Golgi's methods. Some of the larger isolated processes in the basement substance show with the very highest powers an irregularity of outline of the process. These processes show minute nickings or a jagged outline of the edges. In one such process a clear vesicle was found like those described in the bodies of the degenerating ganglion cells (Fig. 4, *a*).

As regards the distribution of these ganglion-cell changes, they are not especially concentrated about the region of the foreign body, but are scattered all through the sections, even to the lateral boundaries.

There is no positive support for making statements about the duration of the ganglion-cell degeneration, but the impression is conveyed that the process is an exceedingly slow and gradual one. The cells do not show the swollen and other appearances of rapid degeneration such as are seen in the acute processes of the spinal cord. It seems probable that these damaged cortical cells may persist for a long time in the earliest

stages of degeneration before advancing to the later or final stages.

The Changes in the Neuroglia.—There is a limited and very early stage of hyperplasia of the neuroglia tissue. This statement, however, can be better relied upon if the excessive difficulties attending the detection of this stage of a slowly growing neuroglia-hyperplasia are indicated. The neuroglia cells appearing in ordinarily stained sections as small round cells, are very profusely scattered throughout all of the cortical layers except in the barren layers, and their true form is only apparent by Golgi's methods. Then again, these cells are irregularly distributed, and vary somewhat in different cortical regions. In some layers they are very thickly aggregated together, and in other layers more sparsely arranged. Thus in this diffusely arranged tissue, without contrast to the surrounding tissues, in determining a slight increase of newly formed neuroglia cells which look exactly like their surrounding progenitors, we often have an insoluble problem. When the young neuroglia cells have become more mature, and possess a larger cell-body with beginning branches, a new difficulty arises in their identification, for frequently they cannot be distinguished from the surrounding ganglion cells of the same size. So the earlier diffuse increase of neuroglia is unfortunately liable to escape recognition until the process has become fairly extensively developed.

Notwithstanding these difficulties, there are a few places in the sections which show quite distinctly clusters of an increased number of very young and seemingly proliferating neuroglia cells. These are most distinctly seen in the layer of small pyramids. In a few places in this layer there are groups of small round cells which, although not sharply circumscribed, are still so closely aggregated that they stand out more clearly than the remainder of the rather sparsely distributed neuroglia cells of this layer (see Fig. 5). The contrast of the barren layer is also an aid in distinguishing these cell groups. These cells are often arranged in groups of twos or ill-defined strings of four to six in number. In two cells only were positive evidences of mitosis discovered, and these are shown in Fig. 5, *a*, and more highly magnified in Fig. 7, *b*.

In the deeper layers there are some similar groups of increased neuroglia cells, but they are much less clearly defined. Thus the production of neuroglia in the deeper layers is hidden from view, because the normal neuroglia cells are so thickly aggregated that the newly formed cells cannot be distinguished from them. In one single instance in all of the sections, a cluster of neuroglia cells on the edge of the specimen, in the deeper layers, was quite circumscribed from the surrounding cells and grouped differently, and seemed to be a cluster of proliferated young neuroglia cells. These young neuroglia cells at first seem to be indifferent cells. They have a

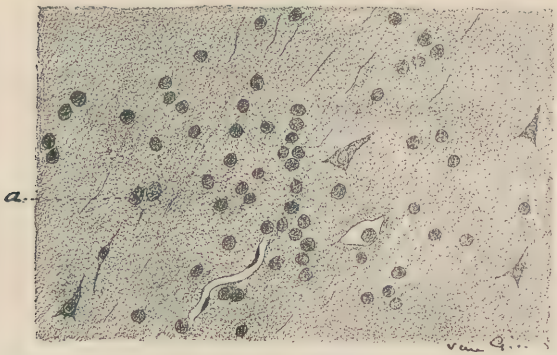

FIG. 5.—A Group of Young Neuroglia Cells Situated in the Layer of Small Pyramids.

thin, spherical envelope of protoplasm, which at first appears to have no processes.

At a later stage of development the protoplasm increases in volume, and they lengthen out into spindle- or oval-shaped masses and send out branching processes. Groups of these more mature neuroglia cells were also found in the sections, and they could be identified most clearly in the layer of small pyramids, because here there was no doubt of mistaking them for small ganglion cells, for the small pyramids were so universally and thoroughly shrunken (see Fig. 6). If there are other groups of these more mature neuroglia cells in the deeper layer, they cannot be distinguished plainly because of their close resemblance to the small or polymorphous ganglion cells.

Fig. 7, at *a*, shows this difficulty of distinguishing newly

formed neuroglia cells from ganglion cells. These two sets of cells seem to be neuroglia cells; they have large, glassy cell-bodies, and suggest a phase of cell division. Both of these two groups of neuroglia cells were found among the larger ganglion cells of the fourth layer, and are significant in evidencing an overgrowth of neuroglia in this important layer of the motor zone. Finally, in a single instance, a very large mature branching neuroglia cell was found in the deeper layers, as shown at Fig. 7, *c*. Lying alongside of this large spider cell are the remains of the nucleus of a degenerated ganglion, which may, perhaps, convey a suggestion as to the destiny of the previ-

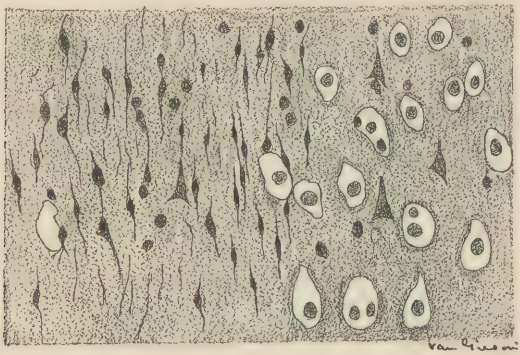

FIG. 6.—A Group of more Mature Neuroglia Cells in the Layer of Small Pyramids. This illustrates the next stage of development of the neuroglia cells from the group in Fig. 5.

ously described small round cells crowding the spaces of the ganglion cell, but there is no real evidence to show that the small round cells in the ganglion-cell spaces ever become large spider cells.

There is then an increase of neuroglia in these sections, and it is of a very early and limited stage of development, and yet the impression is conveyed that only a portion of this growth is apparent in certain favorable situations, as in the narrow layer of the small pyramids. Still there are several indications of neurogliar growth in the deeper layers, as, for example, in Fig. 6, inviting the belief that the process is not limited to the region where it may be recognized most easily, but is a diffuse growth and involves the layers beneath the small pyramids, but possibly to a less extent.

The *neurogliar hyperplasia* is *irregularly distributed* throughout all of the sections, even at a distance from the foreign body, and often occurs in spots or patches. Most of the sections of the depressed region of the cortex show a slight concentration of the neurogliar growth as young, small, round cells, or more mature spindle-shaped cells, scattered about among the lesser pyramids.

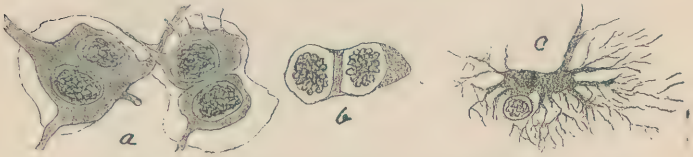

FIG. 7.—Neuroglia Cells from the Deeper Layers of the Cortex. *a*, Indicates two neuroglia cells which seem to be in the process of proliferation; *c*, is a large mature branching neuroglia cell lying alongside of a degenerated ganglion cell which has dwindled away, leaving nothing but an indistinct nucleus; *b*, two young neuroglia cells showing karyokinetic figures; these are the cells indicated at Fig. 5, much more highly magnified.

This growth of the neuroglia, like the degeneration of the ganglion cells, seems to take place very slowly.

The blood-vessels of the *cortex* are normal in structure, but in places they are not properly arranged. In places anastomosing net-works of capillaries penetrate the cortex from the pia mater, and, accompanied by and surrounded by more or less neurogliar increase, appear as wedge-shaped areas in the section. This is shown schematically at *z*, Fig. 2.

Microscopical Examination of Case II.—In this case there is a development of rather a large mass of connective tissue which has altered very materially the structure and topography of the convolutions which it has grown into. In this way the gray matter at the seat of the operation has been irregularly replaced by connective tissue, and has been rather largely converted into neurogliar tissue.

The removed portion was a flattened disk and measured about two ctm. in diameter, and was from five to seven mm. thick; it was hardened in strong alcohol, and the celloidin sections were stained in the same way as in the preceding case.

The specimen consists of two layers, an outer layer of connective tissue and beneath it a layer of damaged cortex. At one side of the specimen a new layer makes its

appearance, from the fact that a bit of the scalp is adherent to the specimen and has been removed with it. Throughout the remaining extent of the specimen the scalp is absent, and the connective-tissue mass referred to is the outermost layer. Sections from the region of the specimen where the scalp is attached show the appearances in Fig. 8. The scalp (*a*), with its clusters of fat-cells and obliquely cut hair-follicles, covers and partly surrounds a bit of damaged cortex (*c*). The scalp shows atrophic changes of a moderate degree, and the attachment to the brain is rather a loose one. The brain, in

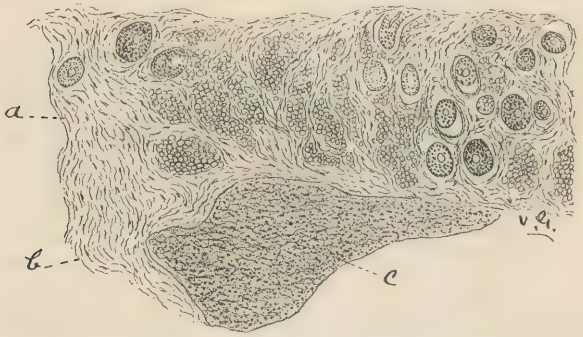

FIG. 8.—A Section through the Scalp in Case II., and Degenerated Cortex beneath, Showing their Loose Attachment.

this particular part of the specimen at any rate, simply lies against the scalp rather than being attached to it, and there are no blood-vessels passing from the one to the other.

A tongue-like projection of rather dense connective tissue (Fig. 8, *b*), passes inward from the scalp at one place—just at the edge of the specimen—and tends to partially surround the degenerated fragment of the cortex. This tongue-like mass blends with, or is perhaps a portion of, the extensive lamina of connective tissue forming the upper layer throughout the rest of the specimen (see Fig. 9).

The bit of cortex lying underneath the scalp is very extensively changed. The ganglion cells are severely degenerated, many of them are reduced to mere hollow shells or skeletons surrounding the nuclei, and many others must have disappeared entirely. There is also a very perceptible increase in the size and number of the

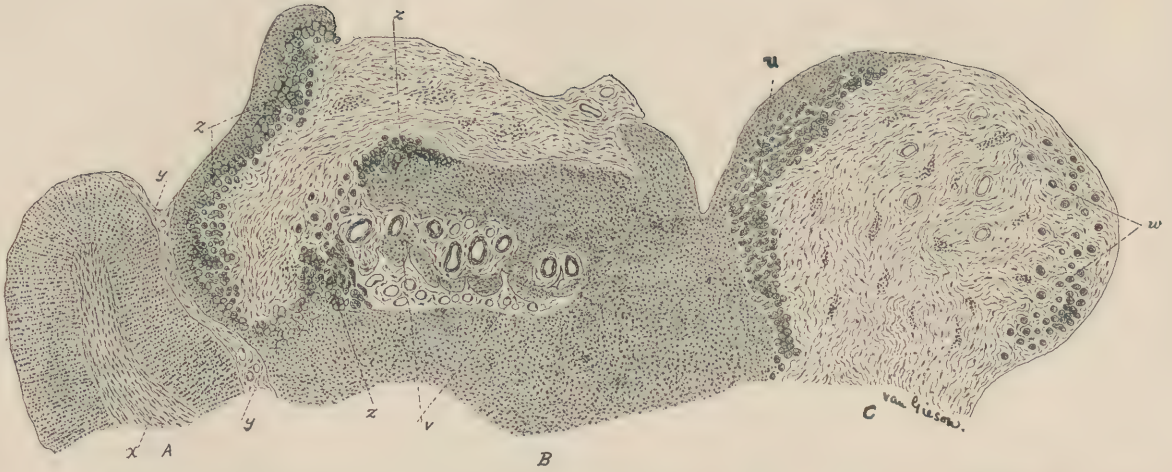

FIG. 9.—From a Section through the Centre of the Removed Portion, Showing the Distribution of the Dense Connective-tissue Masses which Replace Portions of the Convolutions. The convolution *A*, while retaining its normal shape and volume, shows extensive minute structural changes; the convolution *B*, partly replaced by connective tissue, is very extensively damaged in the remaining portions by the neuroglia hyperplasia; at *z*, *z*, *z* the cortex is converted into single or clustered islands of neuroglia tissue; *V* indicates a region where the cortex, converted into neuroglia tissue, is disintegrating and liquefying. The convolution *c* is still more extensively involved by the growth of connective tissue, and at *u* and *w*, again shows the conversion of the cortex into insular masses of neuroglia.

neuroglia cells. Both of these changes have reached such advanced stages that there is no difficulty attending their positive recognition.

Sections through the centre of the specimen show in a general way masses of dense connective tissue which encroach upon and cause material changes in the convolutions, as depicted in Fig. 9. Such a section from the centre of the specimen shows three convolutions, *A*, *B*, and *C*, two of which are involved by the connective-tissue growth, while a third, *A*, has escaped this encroachment.

The convolution *A*, although uninvolved by the connective-tissue growth, and retaining its proper form and volume, is yet considerably changed. The ganglion cells are fairly extensively affected by various phases of a series of degenerative changes. Very many of the cells show the earlier and less well-pronounced stages of the degeneration, while a lesser number show the more extensive changes in the cell-body tending toward complete disintegration of the cell, as described in the previous case. Altogether the degeneration of the ganglion cells in this convolution is so well marked as to do away with the difficulties attending the recognition of the very early stages of the same process.

The neuroglia of the gray matter do not seem to be increased to any appreciable extent, but the white matter (*x*) is quite extensively involved by a growth of spindle-shaped and branching neuroglia cells. At the apex of the convolution this neuroglia increase extends a little distance into, or seems to follow the passage of, the nerve-fibres into the gray matter.

In the convolution *B*, the dense growth of connective tissue appears, hollowing out the apex of the convolution, and in many places at its junction with the gray matter fashions the latter into curious little islands or tubular plugs (Fig. 9, *z*, *z*, *z*) often more or less surrounded by connective tissue. The brain tissue of the convolution *B* shows a tendency to become converted into neuroglia tissue, especially in the regions *z*, *z*, *z*, where it consists entirely of neuroglia cells with their branching and tangled processes. In the other portions of the convolution there are quite a few degenerated ganglion cells

scattered about among the proliferating or much increased neuroglia elements, so that the rest of the entire convolution is extensively damaged, and the gray matter cannot be distinguished from the white matter except by the presence of the degenerated ganglion cells.

In the convolution *C*, there is a still greater production of connective tissue and a corresponding diminution in the substance of the cortex. At (*u*) the plane of the section has cut the insulated masses of the cortex lengthwise, so that they appear as rather short convoluted cylinders. Some of these cylinders or plugs persist, completely isolated in the dense connective tissue, as little islands of neuroglia tissue (see Fig. 9, *w*).

When the process of insulation of clustered or isolated masses of the cortex is examined with more detail, in a section at the junction of the connective-tissue masses with the cortex, the features shown in Fig. 10 (taken from the convolution *B*) are presented. In such a section four tolerably distinct layers may be recognized. Proceeding from without inward toward the brain, there is at first the very thick extensive layer of dense connective tissue which has already been topographically studied in the preceding paragraph. The first layer is apparent in Fig. 10 at *a*. It is composed of ordinary connective tissue, rather densely arranged, with its fibre bundles interlacing and running in various directions, and contains very few blood-vessels. The second and next layer is a vascular zone and lies immediately beneath the preceding layer. It is composed of a congeries of thin-walled vessels, which give the impression that many of them are newly formed. This second layer is shown in Fig. 10, at *b*, *b*, *b*, and *c*. Still proceeding inward, the third layer, *d*, *d*, *d*, is the one which consists of the clustered or discreet islands and plugs of neuroglia tissue. Finally, the fourth and last layer is the compact substance of the brain, *e*, *e*, which has its neuroglia much increased, and its ganglion cells quite thoroughly replaced or degenerated. In fact, this fourth layer represents brain cortex largely converted into neuroglia tissue.

Now, the third layer of the insular masses seems in great part, if not entirely, to owe its origin to the agency of the newly formed vessels of the second or vascular

layer. These thin-walled vessels appear to pass into the compact brain substance, and by anastomosing with each other and by sending off secondary offshoots, surround little island-like masses of the brain which has already been largely converted into neuroglia tissue. In Fig. 10, at *f*, the early stages of such a process can be observed. Here are delicately walled small vessels or capillaries growing into the brain, and by the course they

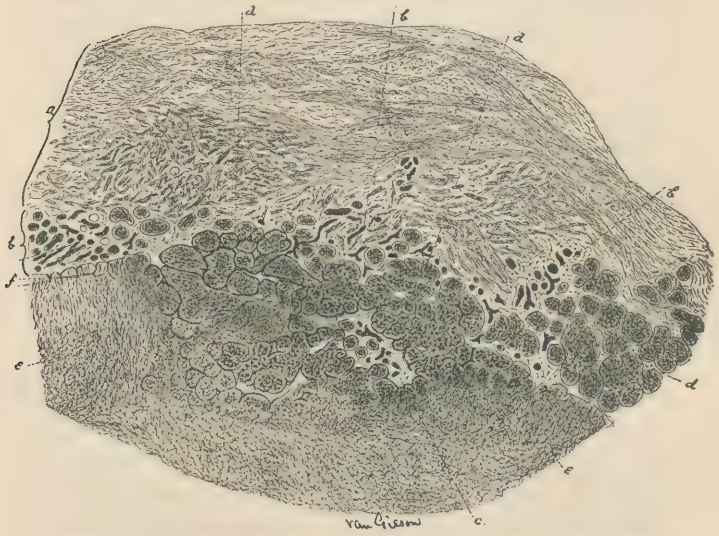

FIG. 10.—(From the Convolution *B*), shows a more detailed view of the formation of islands of neuroglia tissue from the changed cortex at the junction with the connective-tissue masses, and consists of four layers, viz. : *a*, layer of dense connective tissue ; *b*, *b*, *b*, vascular layer ; *d*, *d*, *d*, and *c*, layer of clustered neuroglia islands ; *E*, *E*, the compact cortex, largely converted into neuroglia.

pursue and by their tendency to unite with each other, they exclude little island-like masses of the cortex.

Thus the layer of insular neuroglia masses seems to be formed from the compact brain by a peculiar segregating action of newly formed blood-vessels. It is further to be noted that, following quite universally the layer of insular neuroglia masses, there is always this vascular zone, intimately associated with them, and it lies between the dense masses of connective tissue and the islands. So the capillaries seem to determine the separation of neuroglia masses from the changed solid cortex, and mould them into tiny islands or short cylinders (Fig. 11). In Fig.

11 (taken from the region *C*, in Fig. 10) a still more detailed exposition of this relation of the vessels to the neuroglia islands is presented. Here the capillaries, one of them collapsed at *y*, *y*, are seen surrounding the plugs and islands. But at *x*, *x* is shown a stage of subdivision of one of these islands by a solid protoplasmic offshoot of a capillary destined to become hollowed out into a new blood-vessel. Care was taken not to confound this solid protoplasmic process with a collapsed capillary, and it can be observed how it would divide the mass in two nearly equal parts, by uniting with the opposite capillary.

Some of these masses of neuroglia persist as isolated little islands even in the midst of dense connective tissue, as shown in Fig. 12. In such instances connective-tissue fasciculi have apparently followed the course of the

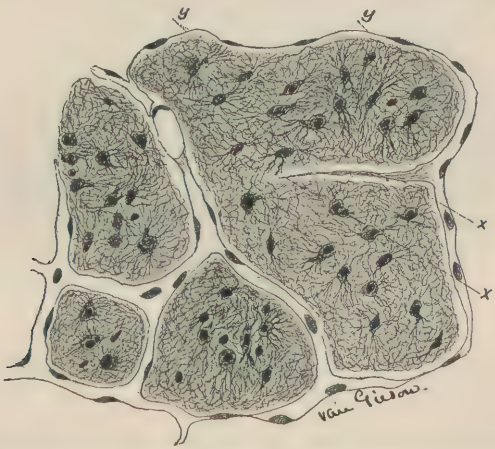

FIG. 11.—The Relation of the Capillaries to the Insular Masses of Neuroglia. *y*, *y*, is a collapsed capillary; *x*, *x*, indicates a solid protoplasmic offshoot of a capillary, which is destined to become a new vessel and subdivide one of the insular masses into two portions.

capillaries and have grown about the neuroglia islands. Fig. 12 also shows very faithfully the minute structure of these islands. They consist of rather large, glassy neuroglia cells completely enveloped by their own tangled and matted process. In the mass indicated at *A*, the filamentous processes are cut vertically, and at *b*, two tongue-like processes of neuroglia pass beneath connective-tissue fascicles and fill up two inter-fibrillary spaces. The vessel *c* has a thickened or hyaline wall.

Finally, it is to be noted that the cortex, for some little distance surrounding the connective tissue growth, is considerably damaged by a degeneration of the ganglion cells and an overgrowth of neuroglia.

Remarks.—It is exceedingly difficult to follow out the connected history of this process in Case II., without having the opportunity to study the whole of the involved territory of the brain. The rather limited material examined in the removed specimen fails to show the lateral

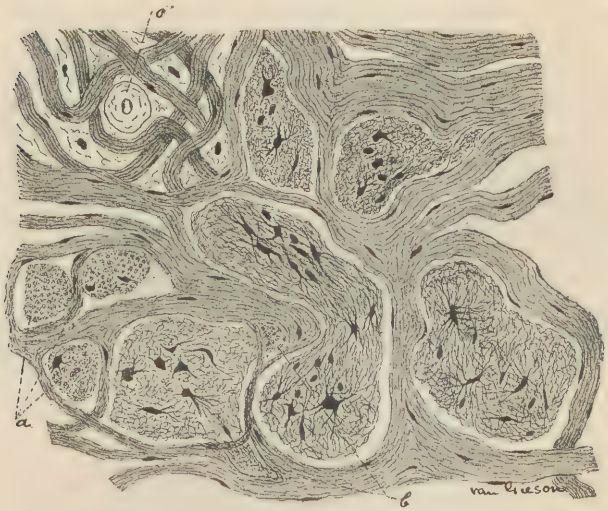

FIG. 12.—The Minute Structure of these Neuroglia Islands and their Persistence in the Midst of Dense Connective Tissue. At *a* the filaments of the neuroglia cells are cut transversely, and at *b* two tongue-like extensions of a neuroglia island fill up two inter-fibrillary spaces.

border zones of the process, or the relations of the brain membranes, and in general the whole topographical distribution of the lesion. Thus, there is no distinct clew to the origin of the process, or to the formation of the cyst discovered at the operation. Still it may be said that this dense mass of connective tissue seems to have grown down rather slowly, apparently from the membranes of the brain, and by disintegrating portions of the brain beneath has contributed to the formation of the cyst, for there is in places distinct evidence of disintegration of the cortex beneath the overgrowth of connective tissue. If in the nature of a scar from the operation, this considerable mass of connective tissue, and its effect on the surrounding

brain tissue, is very interesting in showing what may happen in the healing process of operations on the brain.

It is to the minute changes in the ganglion cells and the neuroglia that attention is more particularly directed, rather than to the grosser changes in these two cases. In reviewing Case I., these delicate and slightly marked changes on the cortex consist of a little increase in the neuroglia cells, a part of which can be seen on favorable spots only, and a gradual death of the ganglion cells. In describing these two sets of changes in Case I., it was frequently remarked that these minute lesions were of a very early stage of development, and not very striking in the section. This is true as far as our rather coarse perception of them under the microscope is concerned, but when we consider the interference of the mechanism of the cortex by these lesions, they are advanced, intense, and very pronounced. Such changes as described in Case I., if transferred to a comparatively inferiorly-constructed organ like the liver, we should hardly associate them with any symptoms; but taking place in the highly-specialized brain cortex, and in the well-known motor portion, they become invested with a great importance in regard to the production of symptoms.

It does not at all convey the full import of the meaning of these minute cortical changes detailed in Case I., if we finish with them, in summing up the lesions, by simply saying that there is a slight increase of neuroglia and a degeneration of scattered ganglion cells. It is only after the reader conceives of the many initiations or modifications of those molecular changes or nervous impulses which sweep to and fro in the tangled cortical network of cell dendrites and terminal fibre arborizations, that he appreciates more vividly the true meaning of these delicate changes which appear so slightly marked under the microscope.

When we compare the second with the first case, we find the same sort of minute changes in the ganglion cells and neuroglia, in the convolutions around the lateral margins of the mass of connective tissue, and in addition, changes in the white matter of such convolutions. There is then a precisely similar condition of portions of the motor convolutions in both of these cases, consisting in minute

changes in the neuroglia and ganglion cells. In the first case the condition is referable apparently to the foreign body and the trauma. In the second case the influence of the connective-tissue mass seems to have induced the condition in the neighboring convolutions.

It seems to me that this gradual death of the ganglion cells in the motor zone, especially the very large motor cells, together with the growth of neuroglia, in both the gray and white matter explains the symptoms of epilepsy very well, and much better than some of the other described changes, as for instance the lesions of the cornu ammonis, which certainly have very little causal relation to the symptoms as far as localization is concerned. Of course these are traumatic cases, but this ought not to preclude regarding this disease process in the cortex in a significant relationship to the symptoms of epilepsy. For trauma might well enough be only one of several conditions which produce this same sort of disease-process in the motor cortex, resembling somewhat a very common form of inflammation of the internal organs exemplified by chronic diffuse nephritis, which arises a variety of conditions for the most part not understood.

Nevertheless, while it is very tempting to see in these lesions a basis for the motor phenomena of epilepsy, there are not facts enough in these two isolated traumatic cases to say anything positive about this relation. Still I venture to think that such changes as described in these cases are very suggestive lines along which to work out the true lesions in idiopathic epilepsy. Idiopathic epilepsy certainly seems to be a disease of the motor zones, and it behaves like an organic disease with definite lesions behind it.

A question which presents itself in connection with Case II. is, how often do the operations on the brain cortex leave an irritating scar which tends to produce lesions in the surrounding brain tissue like those described in the convolution *A*, Fig. 9? If trephining the motor cortex for traumatic epilepsy leaves a cicatrix irritating the neighboring convolutions and changing them like this convolution *A*, the epileptic symptoms ought to return in a certain length of time after the operation.